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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/173,821	10/16/1998	PHILIP SPENCER RUDLAND	32040PCTUSA-	4674

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	2

DATE MAILED: 02/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/173,821	Applicant(s) RUDLAND ET AL.	
	Examiner Sumesh Kaushal	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-9,13 and 15-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7-9,13,15-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/21/01 has been entered.

Claim 6 was canceled.
Claims 1, 7, 8, 13, 17, 18, 25, 29, 30, and 32 were amended.
Claims 1, 4, 7-9, 13, 15-32 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The references cited herein are of record in a prior Office action.

Applicant's response filed on 11/21/01 have been fully considered but is found unpersuasive for the reasons of record as set forth in the earlier office action (Paper No.20, 11/21/01).

Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 recites limitation "ECACC Accession number 96092454" which is a NF2C cells encoding NS-LtsA58δt transgene (spec. page 33, line 2-3), whereas claims 7-8 are drawn to a neuronal cell line comprising and C-erb-B-2 or TGFα transgenes.

Claim Rejections - 35 USC § 112

Claims 1, 4, 7-9, 13, 15-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic rats encoding in their genome a transgene construct comprising i) NS-LtsA58δt (*human neurofilament gene promoter*), ii) MMTVLTR-TGFα or iii) MMTVLTR-C-erb-B-2, does not reasonably provide enablement for a neuronal cell line obtained from a transgenic rat, a transgenic rat, and the method of producing the same wherein the transgenic rats (as claimed) comprises any and all cell type specific promoters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the earlier official action mailed on the 05/23/01.

The instant claims are drawn to a neuronal cell line(s) derived from transgenic rat(s), and the method of producing the same wherein the transgenic rats comprising a conditional oncogene, transforming gene or immortalizing gene or a cell cycle affecting genes (wherein the gene is SV40A58, TGFα or C-erb-B-2) and a cell specific promoter (where in the tissue specific promoter is human NF-L promoter gene).

The applicant argues that recent amendment of claims 1, 13, 17, 25, 29-30 and 32 would obviate the instant rejection because after the amendment claims specifically recites conditional oncogene or transforming gene or immortalizing gene or cell cycle affecting gene are SV40tsA58, C-erb-B-2 and TGFα.

However, this is found unpersuasive because the scope of instant claims encompass a neuronal cell line or transgenic rats comprising any and all cell type specific promoters. At best the instant specification is only enabled for transgenic rats encoding in their genome NS-LtsA58δt containing a human neurofilament gene promoter NF-L, which is neuronal specific (spec. page 30, table-3), and MMTVLTR-TGFα and MMTVLTR-C-erb-B-2 which contain MMTV-LTR promoter, which are mammary gland specific (spec. page 50, table-6). In addition

the specification teaches the development and breeding of neuronal cell line NF2C derived from NF-Lts58Uδt transgenic rats (page 30 table-3, page 28, table-2).

It is important to note that, the scope of the instant claims include rats encoding any and all cell type specific promoters operably linked to SV40tsA58, C-erb-B-2 or TGFα. At best the instant specification only teaches human neurofilament gene promoter NF-L, which is neuronal specific. In addition, the scope of instant claims also encompasses a neuronal cell line derived from a transgenic rat encoding the TGFα and C-erb-B-2 transgenes. However, the specification only teaches transgenic rates encoding MMTVLTR-TGFα and MMTVLTR-C-erb-B-2, which contain MMTV-LTR promoter (spec. page 50, table-6). The specification further disclosed that MMTVLTR-TGFα and MMTVLTR-C-erb-B-2 transgenes were expressed in variety of tissues including epithelial cells, salivary glands, kidney and spleen (spec. page 60, para.3). The instant specification fails to disclose that the expression of MMTVLTR-TGFα and MMTVLTR-C-erb-B-2 transgenes are only limited to neural cells. It is unclear how one skill in the art would conclude that the MMTVLTR-TGFα and MMTVLTR-C-erb-B-2 transgenes construct would lead to neural cell type specific expression of these transgenes.

The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. The transgene expression and physiological consequences of transgene products are not always accurately predictable because cis elements are controlled differently by various transacting factors in the genome of an animal. Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (see Wall RJ Theriogenology 45:57-68, 1996).

Therefore, the skilled artisan at the time of filing would be lacking a reasonable expectation of success for making neuronal transgenic cell lines derived from transgenic rat(s),

comprising any and all cell type specific promoters, without having to engage in an undue amount of experimentation for the breadth of the claims.

Claim Rejections - 35 USC § 103

Claims 1, 4, 7-9, 13, 15-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Noble at al (WO 91/13150, 1991), Stocklin et al (J. Cell Bio. 122(1):199-208, 1993), and Moses JH (Br. J. Cancer. 69(21):1, 1994) in view of Reeben et al (Biochem. Biophy. Res. Com. 192(2):465-470, 1993) in view of Leder et al (US Pat No. 5087571, 1992) and further in view of Hammer et al (US Pat. No. 5489742, 1996), for the same reasons of record as set forth in the earlier official action mailed on the 05/23/01 +.

The instant claims are drawn to a neuronal cell line(s) derived from transgenic rat(s), and the method of producing the same wherein the transgenic rats comprising a conditional oncogene, transforming gene or immortalizing gene or a cell cycle affecting genes (wherein the gene is SV40A58, TGFα or C-erb-B-2) and a cell specific promoter (where in the tissue specific promoter is human NF-L promoter gene).

The applicant arguments filed on 05/23/01 are identical to the response filed on 03/09/01 (see pages 4-9). The applicant argues that the claimed invention is not rendered obvious by the cited art. The applicant further argues that one ordinary skill in the art with the motivation to combine the refereces and would not have any reasonable expectation of success. The applicant further argues that it is an unexpected result that human NF-L promoter when introduced into transgenic rats, as oppesed to mice, would result in a completely unique tissue specific expression in the brain of transgenic rates.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Noble et al teaches transgenic animals and cell lines from any cell type of the animal body, wherein the cell line comprises SV40tsA58 immortalizing gene (fig-1; page 34, line 1-20, page 35-40, page 50, line 19, page 53, line 22, page 56, line 16, page 59, example-3, page 61 example-4 page 64, example-5 page 69, example-6, page 74, example-7). Noble at clearly teaches the making of cell lines derived from the central nervous system, for example the making of astrocytes and glial precursor cell lines (see page 53 line 22, page 61 example-4, page 64 examle-5).

Stocklin et al teaches a transgenic mice wherein the human c-erbB-2 is operably linked to MMTV enhancer/promoter sequence wherein the transgene is expressed in kidney, lung, mammary, muscle, spleen, brain and liver cells (page 200, col.2 para.5, page 201, fig-1, col.2 para 2-3, page 202, table-II).

Moses teaches a tarnsgenic mice expressing a gene encoding hu TGF-a under the control of MMTV enhancer/promoter (page 1, s1).

However, Noble et al, Stocklin et al and Mosses does not teach the use of human neurofilament (NF-L) promoter to derive the expression of SV40tsA58, c-erbB-2 and TGF-a genes.

Yazdanbakhsh et al teaches human neurofilament (NF-L) promoter which regulates neuronal-specific expression (page 455, abstract). Yazdanbakhsh et al clearly teaches that the highest level of transgene expression ocurs in the brain, including that the regulatory sequences that direct tissue-specific expression are present on hu NF-L fragment used (see page 459, col.1 line 8, fig-4).

Leder et al teaches method of providing a cell line from a transgenic mice encoding a transforming oncogne operably linked to mammary specific promoter MMTVLTR (col.4 line 13-22, col.9 line 11-20). Leder et al also teaches the use of transgenic mice for testing a material suspected of being a carcinogen (col.8 line 50-68). The cited art also teaches a method of testing a material for its ability to confer protection against the development of neoplasms using transgenic animals (col.9 line 1-9).

Although the combination of Noble et al, Stocklin et al, Mosses, Yazdanbakhsh et al Leder et al teaches a transgenic mice and/or cell line and a method of screening carcinogens, wherein in the transgenic cell the human neurofilament (NF-L) promoter to derive the expression of SV40tsA58, c-erbB-2 and TGF-a genes, it does not teach the making of a transgenic rat by super ovulting a female rat by continious supply of FSH hormone..

Hammer et al teaches a method for producing transgenic rats, by super ovulating a female rat by continuous supply of FSH hormone using a mini-pump and introduction of the selected transgene into the fertilized eggs (col.15 line 60-67, col.1, line 1-17).

Thus, it would have been obvious to one ordinary skill in the art at the time of filing to have substituted the transgenic mice (encoding human neurofilament promoter which derives the expression of SV40tsA58, c-erbB-2 or TGF-a gene) as taught by Noble et al, Stocklin et al, Mosses and Yazdanbakhsh et al with a transgenic rat as taught by Hammer et al. It would have been further obvious to test a material suspected of being carcinogen a transgenic rat as taught by Leder. One would have been motivated to do this because rats are widely used in biomedical research, and in addition to transgenic mice, a transgenic rat model would provide a two fold experimental approach for the same transgene.

In addition, the expression of hu NF-L regulated gene expression in the brain of rat is not an unexpected result because Yazdanbakhsh et al clearly teaches that the highest level of transgene expression occurs in the brain, including that the regulatory sequences that direct

tissue-specific expression are present on hu NF-L fragment used (see page 459, col.1 line 8, fig-4). Thus, the invention as calimed is prima facie obvious in view of cited refereces.

†*Considering the unpredictability in the transgenic art[1] the phenotypic traits of the disclosed transgenic rats were distinguishable over the phenotypic traits of the transgenic mice (as disclosed in the prior art of record). However, the instant invention as claimed fails to recite any phenotypic characteristic of the transgenic rats (as claimed), which did not distinguish the instant invention over the prior art of record. Therefore, the instant rejection is maintained and is repeated below for the same reasons of record as set forth in the earlier official action mailed on the 05/23/01.*

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem.Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.

S. Kaushal
PATENT EXAMINER

Scott D. Priebe
SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

[1] *Wall RJ Theriogenology 45:57-68, 1996.*